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A NEW NEONATAL SYNDROME

BY

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During the ten-months period December, 1946, to October, 1947, a new syndrome affecting infants appeared in the nurseries of the Birmingham Maternity Hospital. Eight cases were observed, the predominant feature being a circulatory disturbance in one or both lower limbs, while some cases in addition showed muscular weakness or palsy. The case incidence was sporadic, and on only one occasion was the interval between cases less than three weeks. The aetiology was unknown, and neither the medical nor the nursing staff could recall similar cases. Search for guidance in standard textbooks proved fruitless, and it was concluded that the syndrome must have been caused by some new factor, such as a new line of treatment, that had never before operated.

Case Reports

Case 1.—On April 6, 1947, a 60-hours-old infant was found to have a flaccid paralysis of the right lower limb with apparently complete sensory loss below mid-thigh; the leg was pale and cold and no arterial pulsation could be detected. The appearance suggested an embolism of the common femoral artery, but the exact time of onset was uncertain. Next day the foot was still pale and cold, but the calf showed a mottled cyanosis and in a short time the whole limb became warm and flushed. Patches of local discoloration persisted on the front of the leg, the heel, and great toe, and desquamation was followed by scab formation and a chronic ulcer over the anterior border of the tibia. At 1 month old there was still a small unhealed ulcer, and considerable weakness in the anterior tibial group of muscles. At 2 years old there was a pes cavus, a limp, and poor dorsiflexion of the foot.

In an attempt to elucidate the aetiology the obstetric history was checked in detail. The mother, a primigravida, had been treated in hospital from the 34th to 38th week of pregnancy for pre-eclamptic toxaemia. Labour had been induced surgically, but after three days' inertia delivery had been effected by lower-segment caesarean section under general anaesthesia. The child was asphyxiated at birth, and was resuscitated with oxygen and an injection of nikethamide into the umbilical cord. It weighed 5 lb. 3 oz. (2.35 kg.). It had not been delivered through the incision by traction on one leg, and no injection was recorded as having been given into the buttock. The only conclusion that could be reached was that spontaneous thrombosis or embolism of unknown origin had occurred in the main artery to the limb.

It was then recalled by the ward sister that a somewhat similar though more severe case had occurred a few months previously, and that the child had subsequently died.

Case 2.—On consulting the records it appeared that a child had been delivered spontaneously on Dec. 14, 1946, following surgical induction of labour at 37 weeks for disproportion in a primigravida; the second stage of labour had been prolonged to three hours, and the child, weighing 6 lb. 9 oz. (2.98 kg.), had been born in a state of white asphyxia. Its condition being critical, nikethamide followed by lobeline and a second dose of nikethamide had been injected into the umbilical cord without any immediate effect. Six hours later the right leg was seen to be cyanosed and flaccid, with some oedema of the buttock, and during the next day it became cold and anaesthetic. Gangrene of the extremity developed and the infant died on the eleventh day from peritonitis. Necropsy showed thrombosis of the right common iliac artery and also of the inferior mesenteric vessels; there was gangrene and perforation of the sigmoid colon.

No common aetiological factor could be deduced from these two cases, although it seemed probable that the one was a more severe variant of the other. However, the next three months produced five more cases which, although not so severe, presented sufficient similarity to those preceding to warrant grouping together.

Case 3.—A child was delivered on April 30, 1947, by caesarean section for placenta praevia; a general anaesthetic was used. The child was sleepy and asphyxiated at birth, and three injections of nikethamide were given into the cord before respiration was established. On the second day the left buttock was found to be discoloured and indurated as though severely bruised; there was no concomitant paralysis, and the condition resolved in a few weeks without ulceration. It could easily have passed unrecorded had the previous cases not stimulated interest and observation.

Case 4.—This child was seen on May 25. Labour had been induced at 37 weeks in a primigravida with a posterior position of the occiput, but there was an interval of three days before the onset of labour. Intrauterine infection developed, and eventually a small infant 5 lb. 3 oz. (2.35 kg.) was delivered in a state of white asphyxia. Nikethamide was injected into the cord, and recovery was uneventful until the third day, when an area of discoloration was noticed on the right buttock. This area was indurated as though severely bruised, and the overlying skin became necrotic, to produce an unhealthy ulcer which healed with difficulty in about a month. There was never any demonstrable paralysis.

Two further cases were recorded within 24 hours of each other three weeks later.

Case 5.—A baby born on June 18 was the second child of a woman aged 47; during a difficult forceps extraction of a 9-lb. (4-kg.) infant there was considerable delay in delivery of the shoulders, and the child was born in white asphyxia. Two doses of nikethamide were injected into the umbilical cord. Twelve hours later there was extensive discoloration of the right buttock and right side of the scrotum, and during the next two days the gluteal skin broke down to form an ulcer, and a tense hydrocele developed. Movements of the right lower limb were greatly diminished, and there was temporary palsy of the anterior tibial group of muscles. The gluteal ulcer healed in a month, and leg and ankle movements gradually returned to normal.

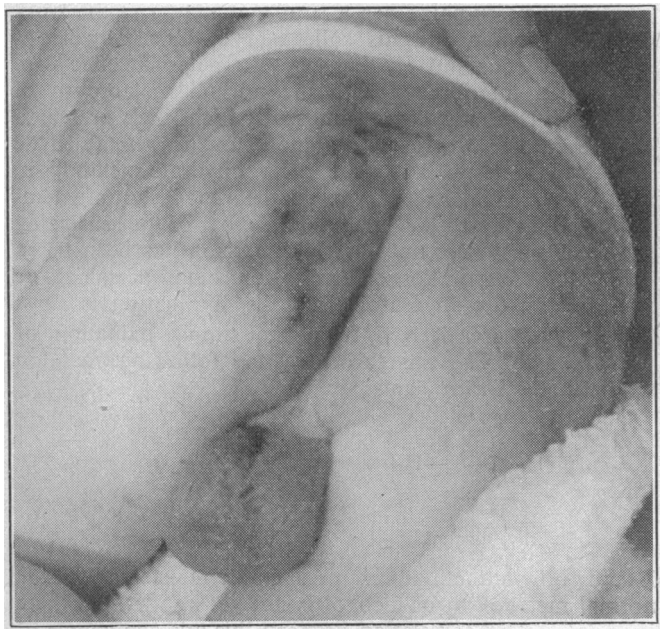
Case 6.—The coincident case was less serious. Labour had been induced at 37 weeks for disproportion in a primigravida, and an infant weighing 7 lb. 3 oz. (3.26 kg.) was delivered with forceps for foetal distress; its condition was only fair, and one injection of nikethamide was given into the cord. Three

days later the typical indurated area of discoloration had appeared on the right buttock, and movements were diminished at the right ankle. There was no subsequent ulceration, and recovery was complete in 10 days.

Case 7.—This child was born on July 16. The infant was delivered precipitately through a rachitic flat pelvis after a long delay at the brim, and its condition was so poor that cerebral haemorrhage was presumed. Its life was twice despaired of, but after three separate injections of nikethamide into the cord respiration was more or less established. Six hours later the child was still cyanosed. There was discoloration of the legs : the left showed a mottled cyanosis of the buttock, thigh, and flank, while the right was pale, atonic, and inactive ; there was also oedema of the left side of the scrotum. Within an hour the pallor of the right limb had been replaced by deep cyanosis, but the child died within 24 hours and no further changes were recorded. Necropsy revealed cerebral haemorrhage and atelectasis with no demonstrable thrombosis or embolism in the main arterial tree of either lower extremity.

Following this case a tentative diagnosis was propounded, and it was hoped that further cases might be avoided. However, the arrival of a new resident two months later was followed by the eighth and final case.

Case 8.—This child was born on Oct. 1. 1947. Caesarean section had been performed on account of some disproportion and inertia, and the child's condition was poor enough to require nikethamide for resuscitation. Within seven hours the left buttock was cyanosed and mottled, the left side of the scrotum was discoloured, and the left leg was pale and atonic (see Fig.). The leg regained full movement within a few days, but the gluteal skin broke down to produce an ulcer, which healed in a few weeks.



Case 8. The area of discoloration of gluteal and scrotal skin is limited almost exactly by the midline of the body. The marks on the lateral aspect of the right buttock have been produced by pressure from the napkin on which the infant was lying.

Discussion

To summarize these eight cases, we have a neonatal condition that has apparently not been previously recorded ; it is probable that cases of little severity have escaped notice in the past, and in fact search in the hospital records has disclosed reference to one such case in 1945. The chief characteristics include the onset of vascular disturbances shortly after birth in one or both lower extremities, with a predilection for the gluteal region, and sometimes a flaccid paralysis of the limb. In one infant there was a fatal issue from cerebral haemorrhage ; in another the inferior mesenteric vessels were affected and the child died from peritonitis ; in a third there was residual paralysis of the anterior tibial group of muscles. All the remainder recovered fully.

After the occurrence of the seventh case a determined effort was made to establish a diagnosis, and various theories were put forward. The unilateral bruising of the buttock suggested thrombosis or embolism of the inferior gluteal artery, which in foetal life represents the main arterial axis of the lower extremity. It is the chief branch of the hypogastric, which continues as the umbilical artery ; the external iliac artery is very much smaller. The inferior gluteal artery contributes the chief blood supply to the sciatic nerve. Embolism was considered improbable on account of the bilateral effect in Case 7 and the mesenteric lesion in Case 1. No cause could be adduced for a primary arterial thrombosis. Injection of vitamin K into the infant's buttock was disproved. The obstetric procedures were so diverse, including spontaneous, forceps, breech, and caesarean deliveries, that there seemed small chance of finding a common factor. However, it was observed that all infants had been born in a state of white asphyxia, and all had required at least one injection of nikethamide for resuscitation. Speculation was aroused upon the possibility of an intravenous injection being responsible for an arterial lesion, when it was suddenly realized that in all probability the injection had been given on occasion into an umbilical artery.

The resuscitation of the newborn is always an emergency procedure, and if it should follow operative delivery the obstetrician may still be engaged in the treatment of the mother. In consequence, the anaesthetist or a junior hospital resident may be instructed to inject " nikethamide into the cord," by which it is intended that 0.5 to 1 ml. of nikethamide shall be injected into the umbilical vein and milked down the cord to the umbilicus. Instead of the familiar engorged cord with a prominent distended vein and two smaller encircling arteries, there will probably be a practically avascular structure in which two dark vessels are dimly discernible. The operator, unfamiliar with the appearance of the cord in states of shock, and anxious to discharge his duty rapidly, may select a vessel and puncture it with difficulty ; whichever he selects will be wrong, for the vein is empty, transparent, and practically invisible, and the injection will have been made into an artery.

It is my belief that in the past this accident has been by no means uncommon, and that the production of a pathological lesion depends upon three factors. The volume of injected fluid and the vigorous nature of the " milking " process will determine how much nikethamide enters the foetal hypogastric arteries, while the height of the infant's systolic blood pressure will decide how far the retrograde injection advances before being swept peripherally in the arterial stream. The actual pathology might be an arterial spasm with ultimate thrombosis similar to the condition in the upper extremity following accidental intra-arterial injection of anaesthetic solutions. The occurrence of a bilateral case may be explained by the use of both umbilical arteries, while the massive effect in Case 1 followed a triple injection —enough to fill the common iliac artery and overflow into the aorta and inferior mesenteric. It is hardly surprising that the notes record " no immediate improvement."

It may be argued that the above hypothesis is mere conjecture supported by circumstantial evidence, and it must be admitted that proof is still lacking. An attempt has

been made to demonstrate the relevant arterial distribution by injecting methylene blue into the umbilical artery of a living anencephalic foetus, but without success. Experiments have been made elsewhere to reproduce the lesion in cats, but no positive result has been obtained. The difficulty of such experiments lies in the fact that the injection must be made against the full force of the neonatal blood pressure, and the fluid is thus unlikely to travel so far in a retrograde direction as it would when the subject was shocked or gravely asphyxiated. However, it is of some significance that after explanation of the danger of intra-arterial injection to the resident staff no further cases were recorded; and those who are uncomfortably aware of having themselves made such an injection testify to the extreme facility with which it may be made in moments of stress and shortage of sleep. There is no satisfactory explanation of the variable interval between injection and discovery of the lesion (6–60 hours), and an inexplicable fact is the sudden appearance of this series of cases in a hospital in which the use of nikethamide by injection into the umbilical cord has been an integral part of the routine for neonatal resuscitation for several years.

Summary

A new syndrome is described, comprising arterial lesions with occasional paralysis in the lower limb of the newborn.

Eight cases are recorded as having occurred in a period of 10 months at a busy maternity hospital.

The aetiology of the condition remains unproved. It is suspected that the lesions may be due to injection of drugs into an artery in the umbilical cord. The evidence in favour of this theory is discussed.

I am deeply indebted to Dr. Frances Braid for her interest in these babies and her stimulating encouragement. I wish to thank Dr. Hudson, of the Walton Hospital, Liverpool, for details of a similar series of cases, and the staff of the Birmingham Maternity Hospital, under whom the cases were admitted, for permission to publish.

A number of Government scholarships have hitherto been available to selected nurses who wished to train as nurse tutors. The assistance given has covered the training and examination fees and the cost of books, and provided an allowance of £150 for the period of training. The Ministry of Health has decided to end this arrangement and to substitute the following. Nurses, both male and female, who are accepted by training institutions for training as nurse tutors should be granted leave on full pay, including emoluments where appropriate, for the period of the training. The nurse would be required to pay the full cost of the training, including examination fees and books. The courses cover an academic year and begin in the latter part of September or early October. The recognized institutions which will be running courses next term are: Battersea Polytechnic, Battersea Park Road, London, S.W.11 (40 places); King's College of Household and Social Science, Campden Hill Road, London, W.8 (20 places); Royal College of Nursing, 1A, Henrietta Place, London, W.1 (36 places); University College, Hull (12 places). The fees for the courses vary from £20 to £50. Applicants must (*a*) be registered in the General Part of the State *Register*, or the Part of the *Register* for Male Nurses (General Trained); (*b*) have had at least three years' experience in nursing in hospital since registration in any Part of the *Register*, including at least one year as a ward sister (or corresponding rank in the case of a male nurse) in an approved training school; (*c*) satisfy the training institution that their general education is such as to justify taking up training. Where an applicant is registered both as a general trained nurse and as a mental nurse or nurse for mental defectives, but has not had a year's experience in charge of a ward, the applicant must have post-registration experience, satisfactory to the General Nursing Council, in an approved training school for a period of at least four years.

TETRAETHYLTHIURAMDISULPHIDE* IN THE TREATMENT OF ALCOHOLICS

BY

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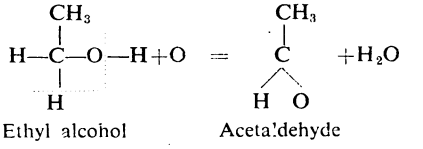
So numerous have been the drugs and techniques used and abused in the age-long struggle against alcoholic excess that one naturally is wary about recommending any new preparation. Yet tetraethylthiuramdisulphide, with the structural formula of $(C_2H_5)_2.N.\overset{\overset{S}{\|}}{C}-S.S-\overset{\overset{S}{\|}}{C}N(C_2H_5)_2$, recently introduced by Dr. Erik Jacobsen, of Copenhagen, shows such promise that it merits extended trial so soon as it becomes readily available to the medical profession in this country. Adequate samples were placed at my disposal upon request, and the following preliminary report shows the advantages derivable from its administration.

The Drug's Action

Before relating these it will be of interest to expound the pharmacological basis of the drug's action. For many years it has been known that certain substances—e.g., cyanamide and the fungus *Coprinus atramentarius*—though innocuous to man when taken alone, yet gave rise to unpleasant symptoms when alcohol subsequently was consumed. Tetraethylthiuramdisulphide has a similar action, and the work of Dr. Jacobsen and his colleagues in Copenhagen has shown fairly conclusively that these characteristic effects are due to an interference with the normal metabolism of alcohol in the body, so that unusually high levels of acetaldehyde become present in the blood stream. Acetaldehyde is a normal intermediate stage in carbohydrate metabolism, and after alcohol its presence in the blood shows a temporary slight increase. When any member of the sensitizing group of substances now under discussion has been taken before the consumption of alcohol the blood acetaldehyde rises steeply (up to tenfold) and its elimination is slow.

Aldehydes are derived from the simple oxidation of primary alcohols, as is shown by the following equation with structural formulae:



Ethyl alcohol Acetaldehyde

Exactly how tetraethylthiuramdisulphide interferes with the normal metabolism of alcohol is not yet known, but there is an interesting correlation between this and the course of events in vitamin B_1 deficiency. In the latter case pyruvic acid, not acetaldehyde, is the stage at which metabolism goes wrong. Aldehydes and ketones are closely allied, having the same general formulae $C_nH_{2n}O$. Similarly the aldehydic and ketonic acids are closely related, and pyruvic acid, $H-\overset{H}{\underset{H}{C}}-\overset{}{\underset{O}{C}}-C\overset{O}{\underset{OH}{<}}$, is the simplest of the ketonic acids. Later the relation between the mechanism of the two derangements in carbohydrate metabolism will probably be discovered. Possibly some similar if not identical inborn

*This drug has the proprietary names of "antabus," "antabuse," and "antalco."